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Maternal vaccination: A review of current evidence and recommendations

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**Title: Maternal vaccination: A review of current evidence and recommendations**

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**Abstract**

Maternal vaccination is an effective means of protecting pregnant women, their fetuses and infants from vaccine-preventable infections. Despite the availability of sufficient safety data to support the use of vaccines during pregnancy, maternal immunization remains an underutilized method of disease prevention, often due to concerns from both healthcare providers and pregnant women about vaccine safety. Such concerns have been reflected in the low uptake of the COVID-19 vaccine among pregnant women seen in many parts of the world, which is due to low vaccine confidence among pregnant women, uncertainty among healthcare professionals and poor access to COVID-19 vaccines. Here we present an update of the current recommendations for the use of vaccines during pregnancy, including the evidence supporting the use of novel vaccine platforms. We also provide an overview of the data supporting the use of COVID-19 vaccines in pregnancy and an update of the status of vaccines that are currently under development for use in pregnant women.

## **Introduction**

Pregnancy and infancy are both periods of increased vulnerability to infection.<sup>1</sup> Vaccinating women during pregnancy has been shown to be effective in providing protection against a number of infections in pregnant women, while also providing protection for the fetus and the infant during early life. Despite these benefits, low vaccine confidence remains a significant barrier to vaccine uptake among pregnant women worldwide and has been a particular challenge during the COVID-19 pandemic, which has seen low rates of vaccine uptake among this cohort. While a small number of vaccines are recommended for routine use during pregnancy, there are many vaccines which have sufficient safety data to support their use in pregnant women in appropriate circumstances. In this review we will provide an overview of current recommendations and evidence supporting the use of vaccinations in pregnancy, including recommendations for the use of novel COVID-19 vaccines.

## **The rationale for vaccination during pregnancy**

Vaccinating women during pregnancy has two distinct potential benefits. Firstly, it protects the woman from infections that she may be particularly susceptible to during pregnancy, which in turn protects the fetus from congenital infection and other harmful effects of maternal infection. Secondly, maternal vaccination may be used for the primary intention of protecting the developing fetus and infant from infection during the first months of life, through the placental transfer of neutralizing immunoglobulin G (IgG) antibodies and/or secretory immunoglobulin A (IgA) antibodies in the mother's breastmilk (Figures 1 and 2).

## **Figure 1**

**Figure 2**

The benefit of maternal vaccination for infants was first demonstrated in 1879 when it was recognized that the children born to women immunized against vaccinia during pregnancy were immune to smallpox during early life.<sup>2</sup> Neonatal vaccination is an alternative measure for the protection of infants from infection, however, it relies on the infant's ability to produce neutralizing antibodies and is less likely to be effective in providing protection against pathogens during the first few weeks of life.<sup>3</sup> Importantly, many vaccines are not administered to infants until at least six weeks of age and often require two or more doses before achieving full protection, thus leaving a critical gap where infants are at increased risk of infection. Vaccinating the mother during pregnancy can augment the transfer of maternal antibodies, thus narrowing the "window of vulnerability" to infections and prolonging the period of protection from disease.<sup>1</sup>

There are many vaccines that are currently licensed which provide protective immunity that is beneficial for both mothers and infants, such as combined tetanus, diphtheria and pertussis (although maternal tetanus vaccination is primarily to protect neonates from disease), and influenza vaccines. There are also a number of vaccine candidates currently under investigation that could potentially be licensed for the principal purpose of protecting the fetus and infant from infection, including vaccines which protect against cytomegalovirus (CMV), respiratory syncytial virus (RSV) and Group B Streptococcus (GBS).

**The assessment of vaccine safety in pregnancy**

The first documented vaccine trial in pregnant women was conducted in Papua New Guinea in 1961, during which administration of two or more doses of fluid formalinized tetanus toxoid vaccine during pregnancy was shown to be protective against neonatal tetanus.<sup>4</sup> At the time, United States (US) Food and Drug Administration (FDA) guidelines excluded pregnant women from all drug and vaccine trials, and following the thalidomide tragedy in the 1950-60s, this exclusion was expanded to all women of childbearing potential.<sup>5</sup> This decision was subsequently reversed by the FDA in 1993 after it was deemed that exclusion of this group of women had led to a substantial lack of safety data for a number of drugs in women of childbearing age.<sup>5</sup> Even so, pregnant and lactating women still remain underrepresented among vaccine trial participants.

Generally, vaccines that are considered safe for administration during pregnancy include killed or inactivated virus vaccines, protein subunit vaccines, toxoid-containing vaccines and conjugate vaccines (which includes protein/toxoid, peptide/protein and protein/protein conjugated vaccines). Vaccines which contain live attenuated viruses are generally not considered safe due to the theoretical risk of congenital infection and the potential increased risk of miscarriage. Recent data from a meta-analysis conducted by Laris-González *et al.* however, did not identify any evidence of increased adverse pregnancy outcomes relating to the use of live vaccines during pregnancy, other than for smallpox vaccines (although, the quality of evidence included was low).<sup>6</sup> In certain limited circumstances, a risk-benefit approach may be reasonably taken as to the appropriateness of administering a live vaccine, particularly in situations where the risk posed to the mother is deemed to significantly outweigh the theoretical risks posed to the fetus (discussed in further detail later).

With the advent of novel vaccine platforms such as the messenger ribonucleic acid (mRNA) and non-replicating viral vector platforms used in the production of the COVID-19 vaccines, the assessment of vaccine safety in pregnancy has reemerged as an area of high priority owing to the limited historical data supporting their use. The assessment of vaccine safety in pregnant women requires additional safeguards to ensure pregnancy and neonatal outcomes are appropriately monitored. Knowledge of the background rates of adverse pregnancy and neonatal outcomes among the study population is also needed for accurate causality assessments. This requirement may limit researchers' ability to conduct maternal vaccine trials in resource-limited settings where such data are not routinely reported.<sup>7</sup> In the US, the Vaccine Adverse Event Reporting System (VAERS) is used for post-licensure vaccine safety monitoring, in which data are collected on adverse events post-vaccination, such as stillbirth, miscarriage and birth defects.<sup>8</sup> In a recent study by Moro *et al.*, VAERS reports relating to pregnant women vaccinated between 2000 and 2014 identified only 50 major birth defects and no unusual clusters of birth defects were seen among these reports.<sup>9</sup>

At present, vaccines undergo at least Phase 1 and 2 studies in non-pregnant women of childbearing potential before they become eligible for Phase 1 evaluation in pregnant women. In circumstances where the need for a vaccine is urgent, such as during disease outbreaks, this process can cause an undue delay in providing sufficient safety data to support the use of the vaccine in pregnant and lactating women. Both the STRIVE trial (NCT02378753), which evaluated the rVSV-ZEBOV vaccine against Ebola, and the recently conducted COVID-19 vaccine trials did not initially include pregnant and lactating women.<sup>10,11</sup> In both circumstances, initial vaccine safety data in

pregnancy were collected from pregnant women who either inadvertently or deliberately received the vaccine in/outside of trials, highlighting the need for a more coordinated approach to facilitate the earlier inclusion of pregnant women in these trials.<sup>10,12</sup> Strategies which may enable their inclusion, include the incorporation of developmental toxicology studies into the vaccine programs at an early time point and the early use of vaccine platforms that are already known to be safe in pregnancy.<sup>11</sup>

### **Increasing vaccine confidence among pregnant women**

Low rates of vaccine confidence among pregnant women remain a significant barrier to increasing vaccination coverage among pregnant women, with persistently low rates of vaccine uptake rates during pregnancy seen in the US and many countries worldwide.<sup>13</sup> A systematic review by Kilich *et al.*, which reviewed factors that influenced vaccine uptake in pregnant women, found that the main determinants were awareness of the vaccine, disease severity and susceptibility, vaccine benefits, side effects and risk of harm during pregnancy, history of previous vaccination, and recommendation from healthcare professionals.<sup>14</sup> It is important that pregnant women are proactively offered the vaccine by their healthcare providers and are given ample time and opportunity to communicate any concerns they may have, while also being provided with sufficient information to help them make an informed decision. It is also important that healthcare professionals are provided with the training needed to be able to effectively counsel and support pregnant women through this decision-making process.<sup>15</sup> Additional solutions recommended for increasing vaccine uptake among pregnant women include increased healthcare provider endorsement of the vaccine, increased healthcare provider and patient education as to the benefits of vaccination, improved regulatory processes including more transparent labelling of

vaccines and multichannel approaches which include community education programs and use of media to promote the vaccine.<sup>16</sup> Marginalized members of society, such as members of migrant communities, have also been identified as having lower rates of vaccine uptake, thus it is also imperative that barriers to accessing healthcare are addressed for these women in order to improve coverage rates among this particularly vulnerable cohort.<sup>17</sup> Targeted messaging which specifically highlights the benefits of vaccination during pregnancy may help women to feel more confident in their decision to take up these offers of vaccination.

### **1) Vaccines routinely recommended during pregnancy**

The following vaccines are routinely recommended for administration during pregnancy by both international and national health organizations. A summary of recommended dosing schedules and contraindications is shown in Table 1. A more detailed summary of COVID-19 vaccines available internationally is shown in Table 2.

#### **i) Influenza**

##### **Current recommendation:**

- CDC: One dose of the seasonal influenza vaccine recommended during any trimester of pregnancy<sup>18</sup>
- WHO: Pregnant women should be prioritized to receive the seasonal influenza vaccine (one dose). The influenza vaccine should be made available to pregnant women all year round.<sup>19</sup>

##### **Vaccine coverage among pregnant women:**

- US: 61.2%<sup>20</sup>

- Worldwide: coverage rates vary from 1.7-95%<sup>16</sup>

Many studies have shown that pregnant women are at greater risk of severe disease and death from seasonal influenza than non-pregnant women.<sup>21-23</sup> Similar outcomes were seen during the 2009 Influenza A (H1N1) pandemic, where pregnant women were 7.2% more likely to be hospitalized than non-pregnant women and were also found to have a disproportionally high risk of mortality.<sup>24,25</sup> One recently conducted prospective cohort study also found that pregnant women who were infected with influenza during pregnancy were more likely to experience adverse pregnancy outcomes, including late pregnancy loss (adjusted hazard ratio (aHR) 10.7, 95% CI 4.3 to 27.0) and a reduction in the birthweight of their infants, compared to women who were not infected.<sup>21</sup>

In light of the increased risks posed to pregnant women, the WHO has advised that pregnant women should be prioritized all year round to receive the seasonal influenza vaccine since 2012.<sup>19,26</sup> The inactivated virus vaccine, containing either three (trivalent; TIV) or four (quadrivalent; QIV) strains of the influenza virus, is recommended for administration during pregnancy. The live attenuated influenza vaccine (LAIV), which is administered intranasally, is contraindicated during pregnancy due to the theoretical risk of placental transmission of the virus to the fetus.

There is no current consensus on the optimal gestational timing of vaccine administration. In the US, pregnant women are advised to receive their vaccination in anticipation of the influenza season.<sup>27</sup> One systematic review and meta-analysis found that the rate of seroconversion did not differ significantly among pregnant women

who received their vaccine during different trimesters, although the geometric mean titers of neutralizing antibodies against influenza in cord blood were found to be 1.44 (95% CI 0.95 to 2.44) times higher among women who were vaccinated during the third trimester than those vaccinated in the first trimester of pregnancy.<sup>28</sup> There is, however, evidence that the risk of fetal death and adverse birth outcomes is greatest for women who are infected during their first trimester of pregnancy,<sup>29</sup> strengthening the rationale for vaccinating earlier in pregnancy.

In addition to placental transfer of maternal IgG antibodies, infants may also receive protection from influenza through secretory IgA antibodies present in the vaccinated mother's breastmilk. In a study conducted by Schlaudecker *et al.*, sustained high levels of influenza-specific IgA antibodies were found in the breastmilk of women vaccinated against influenza during pregnancy for up to six months after birth.<sup>30</sup>

## ii) Tetanus

### **Current recommendation:**

- CDC: One dose (Tdap) recommended between 27 and 36 weeks' gestation
- WHO:
  - If previously received 1-4 doses of TT/Td, give one dose at least two weeks before delivery
  - If not previously received a dose of TT/Td or vaccination status unknown, give two doses of TT/Td at least four weeks apart with the second dose given at least two weeks before delivery<sup>31</sup>

### **Vaccine coverage among pregnant women:**

- US: Tdap vaccine coverage 56.6%<sup>20</sup>

- Worldwide: TT2+/Td2+ coverage 72%<sup>32</sup>

Maternal and neonatal tetanus is now largely not seen in high-income nations, but high mortality rates from the disease are still evident among women and children in many low- and middle-income countries (LMICs).<sup>33</sup> In response to this, the WHO launched the Maternal and Neonatal Tetanus Elimination initiative in 1999 in partnership with the United Nations Children's Fund (UNICEF) and the United Nations Population Fund (UNFPA).<sup>34</sup> Since this time, maternal and neonatal tetanus has been eliminated in 47 out of 59 "at-risk" countries identified by the WHO, through a combination of increased maternal and neonatal vaccine coverage, increased disease surveillance and improved hygiene during delivery (Figure 3).<sup>33,34</sup>

### Figure 3

There are four tetanus toxoid-containing vaccines considered safe for use in pregnancy: TT (tetanus toxoid), Td (tetanus toxoid and reduced-dose diphtheria toxoid, Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) and Tdap/IPV (Tdap in combination with the inactivated polio vaccine). TT was previously widely used, however, the WHO now recommends that a tetanus-diphtheria combination vaccine should be administered instead of TT to provide early childhood protection against diphtheria.<sup>35</sup> The WHO recommends that a total of five doses of TT/Td are required to provide protection throughout childbearing years.<sup>31</sup> If the pregnant woman has not previously received any doses of TT, Td or Tdap, or her vaccination history is uncertain, additional doses are recommended after pregnancy to ensure full protection (Table 3).<sup>31</sup> In high income nations where neonatal tetanus has

been eliminated, Tdap or Tdap/IPV is administered during pregnancy with the primary purpose of preventing infant pertussis.<sup>36</sup>

### *iii) Pertussis*

#### **Current recommendation:**

- CDC: One dose (Tdap) recommended between 27 and 36 weeks' gestation
- WHO: National programmes may consider vaccination of pregnant women with pertussis-containing vaccine as a strategy additional to routine primary infant pertussis vaccination in countries or settings with high or increasing infant morbidity/mortality from pertussis<sup>37</sup>

#### **Vaccine coverage among pregnant women:**

- US: Tdap vaccine coverage 56.6%<sup>20</sup>
- Worldwide: data not available

Pertussis is a highly infectious respiratory disease which can cause serious illness in young infants. Pertussis vaccines have been available since the 1950s and their widespread use significantly reduced the incidence of pertussis disease globally. There has been a resurgence of cases of pertussis in many countries, including those with good vaccine coverage, with high rates of disease in infants. In the US, cases of pertussis rose from 7,857 in 2000 to over 48,000 cases in 2012.<sup>38</sup> In 2005, cocooning was recommended by ACIP in response to the increasing number of cases, whereby close contacts of infants were advised to get vaccinated against pertussis, however, this advice was later revised after it was found that cocooning was poorly effective.<sup>39,40</sup> The WHO recommends vaccination of pregnant women as being a more

cost-effective and effective means of prevention of pertussis in infants than cocooning.<sup>41</sup>

Many countries worldwide have introduced pertussis vaccination in pregnancy in order to protect the infant from pertussis disease. While these programs have been shown to be effective in preventing severe pertussis disease in infants,<sup>42-45</sup> there is uncertainty about the best timing in pregnancy to offer vaccination to provide optimal protection. Some investigators have suggested that later administration is preferable in order to coincide with maximal antibody transfer, while others have reported higher antibody titers at birth in babies born to mothers who were vaccinated earlier in pregnancy.<sup>46-48</sup> Studies evaluating the safety of the Tdap vaccine have not identified any serious adverse events associated with its use during pregnancy.<sup>49,50</sup>

Pertussis vaccination in pregnancy results in higher antibody levels in the infant at birth and this persists for at least 2-3 months. Additionally, high levels of pertussis-specific IgA antibodies have been detected in the colostrum of women vaccinated during pregnancy and are detectable in breastmilk for up to eight weeks postpartum.<sup>51</sup>

The increased antibody levels in infants born to vaccinated mothers may lead to a reduced initial response to the infant's own vaccinations against pertussis and diphtheria,<sup>52-55</sup> although this reduction may not have any clinical implication and levels are generally restored following booster vaccinations.<sup>54,56</sup>

iv) COVID-19

**Current recommendation:**

- CDC: COVID-19 vaccination is recommended for all people 12 years and older, including people who are pregnant, breastfeeding, trying to get pregnant now, or might become pregnant in the future<sup>57</sup>
- WHO: WHO recommends the use of the COVID-19 vaccine in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks. To help pregnant women make this assessment, they should be provided with information about the risks of COVID-19 in pregnancy, the likely benefits of vaccination in the local epidemiological context, and the current limitations of safety data in pregnant women. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.<sup>58,59</sup>

#### **Vaccine coverage among pregnant women:**

- US: 31%<sup>13</sup>
- Worldwide: data not available

Data from many countries have identified pregnant women as being at greater risk of severe disease and death from SARS-CoV-2 infection than non-pregnant women.<sup>60-64</sup> Additionally, COVID-19 in pregnancy is associated with an increased risk of adverse pregnancy outcomes.<sup>60,62,65</sup> One large population-based cohort study based in England found that among pregnant women who had COVID-19 at the time of delivery, there was a greater risk of pre-eclampsia/eclampsia (adjusted odds ratio (aOR) 1.57, 95%CI 1.44 to 1.72), preterm delivery (aOR 2.17, 95%CI 1.96 to 2.42) and fetal death (aOR 2.21, 95% CI 1.58 to 3.11).<sup>66</sup>

Among the COVID-19 vaccines which have been licensed for use internationally, there are four main vaccine platforms that have been employed (Table 2). On 9<sup>th</sup> December 2020, the Pfizer/BioNTech mRNA vaccine was granted emergency use authorization (EUA) by the FDA after the Phase 3 study involving 43,000 non-pregnant participants demonstrated 95.0% efficacy against COVID-19,<sup>12,67</sup> and was granted full FDA approval on 23<sup>rd</sup> August 2021.<sup>68</sup> The COVID-19 vaccines manufactured by Moderna (mRNA-1273) and Janssen (Ad26.COV2.S) were granted EUA by the FDA on 18<sup>th</sup> December 2020 and 27<sup>th</sup> February 2021 respectively.<sup>69,70</sup> Given the initial lack of safety data in pregnancy, a risk-based approach to vaccination was initially implemented and clinicians in countries such as the UK and the US were advised to recommend vaccination for “clinically vulnerable” women following assessment of their exposure risk and clinical risk factors for severe disease.<sup>71</sup> In April 2021, the CDC announced that pregnant women who are eligible for the COVID-19 vaccine could receive the vaccines manufactured by Pfizer/BioNTech and Moderna after real world data from 90,000 pregnant women collected through the v-safe COVID-19 vaccine pregnancy registry did not identify any safety signals.<sup>72,73</sup>

There are currently no data to guide recommendations for vaccine administration at a particular gestational age, although in practice, many women receive the vaccine during the second or third trimester as they may wish to avoid any theoretical concerns around vaccination in the first trimester when organogenesis occurs.<sup>74</sup> Recent studies conducted in the US and Israel have demonstrated placental transfer of vaccine-specific anti-SARS-CoV-2 IgG antibodies, and anti-SARS-CoV-2 IgA and IgG antibodies have also been detected in the breastmilk of lactating women who

were vaccinated during pregnancy for up to six weeks after the first vaccine dose.<sup>75–78</sup>

As serocorrelates of disease protection have not yet been defined, the antibody titers required to confer protection against disease in the pregnant woman or in the neonate are not known. Additional data are needed to determine the benefit of maternal vaccination for the developing fetus and infant (which may in turn provide guidance as to the optimal timing of vaccination) and also the long-term safety of these novel vaccine technologies for offspring born to women vaccinated during pregnancy. In February 2021, Pfizer/BioNTech began global recruitment to their Phase 2/3 trial (NCT04754594) evaluating the safety, tolerability and immunogenicity of their COVID-19 vaccine among pregnant women between 27 and 34 weeks' gestation, with trial completion expected in July 2022.<sup>79</sup> Another Phase 2 trial has commenced in the UK in which the optimal schedule of vaccination for pregnant women is being assessed (ISRCTN15279830).

**Table 1. Summary of vaccine recommended for administration during pregnancy in the US (adapted from CDC guidelines<sup>80</sup>)**

**Table 2. Summary of COVID-19 vaccines, evidence of safety and recommendations for use in pregnancy (adapted from Kalafat et al.)<sup>81</sup>**

**Table 3. Tetanus toxoid schedule for pregnant women and women of childbearing age with no or uncertain previous exposure to TT, Td or DTP. Table reproduced with permission from the World Health Organization.<sup>31</sup>**

## **2) Vaccines safe for use in pregnancy under special conditions**

As well as vaccines in routine use in pregnancy, some vaccinations can be used in specific circumstances, for example, in the context of an outbreak, before travelling, or after exposure to an infection. We have summarized the safety considerations and recommendations for use for this group of vaccines below.

### **COMMONLY USED**

#### *i) Hepatitis B (HBV)*

**Vaccine platform:** Recombinant subunit of the surface antigen protein

#### **Safety considerations and recommendations for use:**

There is no evidence that administration of the HBV vaccine in pregnancy prevents infant infection.<sup>82</sup> Hepatitis B vaccination in pregnancy is not associated with an increase in adverse pregnancy outcomes.<sup>83</sup> The CDC recommends that any pregnant patient who is at high risk of contracting HBV or who would like to receive the HBV vaccine can be offered the vaccine during pregnancy.<sup>80</sup>

#### *ii) Neisseria meningitidis (meningococcal)*

**Vaccine platform:** Polysaccharide and conjugate vaccines

#### **Safety considerations and recommendations for use:**

Meningococcal polysaccharide vaccines are safe<sup>84-88</sup>, immunogenic and result in higher antibody concentrations in the infant.<sup>84-88</sup>

Meningococcal conjugate vaccines have not been associated with any safety concerns in pregnancy.<sup>89-91</sup> There is no evidence about immunogenicity or effectiveness when given in pregnancy.

If a woman is at high risk of meningococcal disease or in the context of an outbreak, vaccination can be recommended.

*iii) Polio*

**Vaccine platform:** Inactivated virus, live attenuated (oral)

**Safety considerations and recommendations for use:** The inactivated virus vaccine (IPV) is routinely offered to all pregnant women in the UK and New Zealand (in combination with Tdap vaccine).<sup>92,93</sup> The CDC does not recommend routine administration to women who are not at increased risk of exposure to the disease.<sup>94</sup> The live attenuated preparation is contraindicated for use in pregnancy, although no adverse birth outcomes have been reported in women who received the oral polio vaccine during pregnancy.<sup>95</sup>

LESS COMMONLY USED

*i) Anthrax*

**Vaccine platform(s):** Recombinant protective antigen (rPA)

**Safety considerations and recommendations for use:** No association has been shown between inadvertent anthrax vaccination in pregnancy and risk of birth defects.<sup>96,97</sup> Because of the severity of anthrax infection, it is recommended that pregnant women should receive the same post-exposure prophylaxis as non-pregnant adults, including vaccination. If women are at risk of inhalational anthrax, they should receive anthrax vaccine regardless of gestation.<sup>98</sup>

*ii) Cholera*

**Vaccine platform(s):** Inactivated bacterium (oral vaccine); live attenuated

**Safety considerations and recommendations for use:**

The inactivated vaccine is theoretically safe, as bacteria within the vaccine are killed and cannot replicate and the vaccine antigens act locally on gastrointestinal mucosa and are unlikely to cause systemic toxicity. No increase in pregnancy adverse outcomes in those women who inadvertently received cholera vaccination in pregnancy have been reported in three retrospective studies which included nearly 3000 women in three countries,<sup>99–101</sup> and a further observational study showed no increase in risk of pregnancy loss or of neonatal death.<sup>102</sup> The WHO recommends that pregnant and lactating women are included in cholera vaccination campaigns as there is high potential benefit and minimal potential risk.<sup>41</sup> The inactivated vaccine should also be considered on a case-by-case basis for women who are at high risk for disease. The live attenuated preparation is contraindicated for use in pregnancy.<sup>99–101</sup>

**iii) *Coxiella burnetii* (Q fever)**

**Vaccine platform(s):** Inactivated bacterium

**Safety considerations and recommendations for use:** There are no studies of Q fever vaccines in pregnancy and no official recommendations about their use.

**iv) *Haemophilus influenzae* type b (Hib)**

**Vaccine platform(s):** Polysaccharide and conjugate vaccines

**Safety considerations and recommendations for use:**

Both vaccine platforms are safe, immunogenic and result in increased antibody concentrations in the infant when administered in pregnancy, although conjugate vaccines are preferred because of the higher infant antibody concentrations at birth and at two months of age.<sup>103,104</sup> There is no evidence of effectiveness in reducing

disease incidence in infants.<sup>105</sup> Hib vaccine could be used in pregnancy if considered necessary, however control of invasive Hib disease in many countries is extremely good and thus the need for Hib vaccination in pregnancy is likely to be low.

*v) Hepatitis A (HAV)*

**Vaccine platform(s):** Inactivated virus; live attenuated

**Safety considerations and recommendations for use:**

There is no evidence of an increase in adverse pregnancy outcomes following inactivated hepatitis A vaccination in pregnancy. The inactivated virus vaccine can be used after consideration of the likely risks of exposure.<sup>106,107</sup> The live attenuated preparation is contraindicated for use in pregnancy.

*vi) Japanese encephalitis virus (JEV)*

**Vaccine platform(s):** Inactivated virus; live attenuated

**Safety considerations and recommendations for use:**

There is no evidence about use of the inactivated JEV vaccine in pregnancy. The inactivated vaccine may be considered if travelling to an endemic area where likely to experience significant exposure. The live attenuated preparation is contraindicated for use in pregnancy.

*vii) Rabies*

**Vaccine platform(s):** Inactivated virus

**Safety considerations and recommendations for use:**

Post-exposure prophylaxis: There is no evidence of an increased risk of adverse pregnancy outcome following the post-exposure administration of rabies vaccine, when compared to the background rate of adverse outcomes.<sup>108–115</sup>

Pre-exposure prophylaxis: Although the studies have focused on the administration of the vaccine following exposure, the safety of the vaccine illustrated in these studies would support its use prior to exposure for a pregnant woman at high risk. Given the high case fatality rate for rabies, pregnancy should not be considered a contraindication to post-exposure prophylaxis and may be considered for pre-exposure prophylaxis for women at risk.

ix) *Streptococcus pneumoniae* (pneumococcal)

**Vaccine platform(s):** Polysaccharide (PPSV) and conjugate (PCV) vaccines

**Safety considerations and recommendations for use:**

Polysaccharide vaccines are safe,<sup>116</sup> and increase anti-polysaccharide antibody in infants,<sup>117–124</sup> although there is little evidence that this affects the colonization rates or disease incidence in infants born to vaccinated mothers.<sup>125,126</sup>

There is limited evidence for the use of conjugate vaccines in pregnancy; the only published study showed that infants of vaccinated mothers had an increased incidence of the primary outcome (acute otitis media).<sup>127</sup>

Pneumococcal vaccinations can be used in pregnancy if protection of the woman is considered necessary.

x) *Tick borne encephalitis virus* (TBEV)

**Vaccine platform(s):** Inactivated virus

**Safety considerations and recommendations for use:**

Theoretically there are no contraindications for use of this vaccine in pregnancy, however, there are no studies of TBEV vaccines in pregnant women and no official recommendations for their use.

*xi) Typhoid*

**Vaccine platform(s):** Oral live attenuated; polysaccharide

**Safety considerations and recommendations for use:**

The safety of the polysaccharide vaccine has not been determined but theoretical risk is low so may be considered when benefits are likely to outweigh risks. The live attenuated preparation is contraindicated for use in pregnancy.

*xii) Yellow fever*

**Vaccine platform(s):** Live attenuated

**Safety considerations and recommendations for use:**

There is only a live attenuated vaccine available for the prevention of yellow fever. Live vaccines are usually contraindicated in pregnancy, however, there is some evidence that yellow fever vaccination in pregnancy is not associated with an increased incidence of adverse pregnancy outcomes, although congenital infection is possible.<sup>107,128–130</sup> Use of this live vaccine can be considered if it is thought that the risks of infection outweigh the possible risks of vaccination.<sup>131</sup> If the risks of vaccination are considered to outweigh the risks of yellow fever, but travel is required to an area which requires vaccination, a medical waiver can be issued.

**3) Vaccines currently under investigation**

*i) Group B Streptococcus (GBS)*

547 GBS is one of the leading causes of neonatal sepsis and meningitis globally.<sup>132</sup>  
548 Maternal rectovaginal GBS colonization has also been associated with an increased  
549 risk of preterm delivery and stillbirth, thus, there is a need to protect the fetus, as well  
550 as providing passive immunity to protect infants after birth.<sup>133</sup>  
551  
552 Six capsular polysaccharide serotypes of GBS cause approximately 98% of invasive  
553 GBS disease in neonates (Ia, Ib, II, III, IV and V), with serotype III causing the  
554 greatest proportion of invasive disease.<sup>134,135</sup> In 1988, Baker and Kasper first  
555 demonstrated the feasibility of maternal GBS vaccination, although initial  
556 observations were of poor immunogenicity of their monovalent polysaccharide-based  
557 GBS vaccine, which was targeted against serotype III.<sup>136</sup> More promising results have  
558 been seen with protein-conjugated capsular polysaccharide GBS vaccines, although  
559 the trivalent CRM<sub>197</sub>-conjugated capsular polysaccharide GBS vaccine developed by  
560 Novartis (targeted against serotypes Ia, Ib and III) did not progress past Phase 1/2  
561 studies (NCT02046148). A recent Phase 1/2 trial conducted by Absalon *et al.*  
562 (NCT03170609) demonstrated the safety and immunogenicity of Pfizer's novel  
563 hexavalent conjugate vaccine (GBS6) in non-pregnant adults, with GBS serotype-  
564 specific geometric mean antibody concentrations remaining substantially elevated  
565 among vaccinated groups six months after vaccination (between 10 and 56-fold  
566 higher than placebo group).<sup>137</sup> Pfizer has subsequently commenced commence  
567 recruitment of pregnant women to their Phase 1/2 trial (NCT03765073).  
568  
569 In June 2020, Minervax started Phase 2 trials evaluating their recombinant protein-  
570 based vaccine (GBS-NN), which is based on the highly immunogenic N-terminals of  
571 the AlphaC and Rib GBS surface proteins (NCT04596878).<sup>138</sup> This study will

evaluate the safety and immunogenicity of the vaccine in pregnant women with and without HIV, which will be of particular value in Sub-Saharan Africa where the rates of invasive GBS disease in neonates and HIV among women of reproductive age are both high.<sup>139,140</sup>

*ii) Cytomegalovirus (CMV)*

CMV is a very common infection which usually causes only a mild self-limiting illness in healthy individuals, but which can cause more serious illness in those with reduced immunity and is an important cause of congenital infection if women are infected during pregnancy. Congenital CMV (cCMV) is the most common cause of congenital deafness globally and development of a vaccine is a priority, which was recognized by the US National Academy of Medicine in 2000.<sup>141</sup>

Congenital infection can occur in women who have never had CMV before and who are infected during pregnancy (primary infection) as well as in women who were infected with CMV prior to pregnancy and either have reactivation of infection or are infected with a different strain in pregnancy (secondary infection), although the risk of congenital infection in the infant is greatest in those with primary infection.<sup>142</sup>

These different modes of infection have made vaccine development complex, as has our limited understanding of the exact mechanisms by which maternal immunity protects the fetus. It seems that antibodies are a necessary mediator of protection for seronegative women, however, T-cell responses also play a vital role in suppressing viral reactivation in women who are seropositive,<sup>143</sup> therefore a vaccine which induces both antibody and cellular responses is likely to be needed. Breastmilk can also transfer maternal immune cells to the infant. Leukocyte populations in breastmilk

are distinct from those found in maternal blood with an enrichment of CD8<sup>+</sup> T cells, predominantly of the effector memory subtype.<sup>144</sup> The exact function of these cells in infants is not yet known but evidence from animal models suggests they may be compensating for the infant's immature adaptive immune system as they localize in the Peyer's patches and their cytolytic and inflammatory activity is four times higher than that of the infant's own T cells.<sup>145</sup> There is also evidence that these breast milk CD8<sup>+</sup> T cells may be able to confer passive cellular immunity even after lysis in the infant gut.<sup>146</sup>

CMV vaccine development has been ongoing since the 1970s. Initial efforts were focused on live attenuated strains, the most extensively studied of which was the Towne strain. This was well tolerated in non-pregnant adults but provided only incomplete protection.<sup>147</sup> Following this, a surface protein of CMV, glycoprotein B (gB), was identified and vaccines based on this were shown to produce a good neutralizing antibody response with up to 50% efficacy against disease, however the antibody response was not persistent.<sup>148,149</sup> Subsequently, a pentameric complex was discovered, which is able to produce higher titers of neutralizing antibody than gB vaccines and which has been shown to provide protection against placental transmission.<sup>148</sup> CMV vaccines which are currently in advanced stages of development include a replication defective pentameric vaccine, an adjuvanted gB based vaccine, viral vector vaccines, RNA vaccines and a DNA plasmid vaccine.<sup>150</sup> Moderna completed enrollment into their Phase 2 study investigating the safety and immunogenicity of their CMV mRNA vaccine (mRNA-1647) in men and women of childbearing age in March 2020 (NCT04232280). Enrollment into the Phase 3 study is expected to commence in late 2021.

622

623 iii) Respiratory syncytial virus (RSV)

624 RSV is a major cause of acute lower respiratory tract infection in infants and young  
625 children worldwide.<sup>151</sup> Infants are particularly vulnerable to RSV infection during  
626 early life; one population-based study found that infants aged <2 months old  
627 accounted for 44% of RSV hospitalizations, and very preterm infants (born at <30  
628 weeks' gestation) were three times more likely to be hospitalized than infants born at  
629 term.<sup>152</sup> Treatment of RSV infection is mainly supportive, although palivizumab  
630 (Synagis®), a humanized monoclonal antibody which targets the antigenic site of the  
631 fusion (F) glycoprotein of RSV, has been shown to be effective in reducing the  
632 incidence of hospitalization among high-risk children aged <24 months.<sup>153,154</sup>

633

634 In the 1960s, a formalin-inactivated RSV vaccine was trialed in infants and toddlers,  
635 however, increased rates of hospitalization and deaths due to RSV were seen that  
636 winter among these children due, in part, to the non-protective low-avidity IgG  
637 response elicited by the vaccine.<sup>153</sup> Maternal vaccination is believed to be a safer  
638 means of conferring immunity in infants against the virus, and while a number of  
639 maternal RSV vaccine candidates have been developed, none have yet been licensed  
640 for use. The efficacy of palivizumab against severe RSV infection has identified the F  
641 glycoprotein as a promising vaccine target, however no vaccines have yet shown  
642 sufficient efficacy in disease reduction in Phase 3 trials.<sup>155</sup> One recent Phase 3 trial  
643 investigating the efficacy of administration of the Novavax recombinant RSV fusion  
644 nanoparticle vaccine between 28 and 36 weeks' gestation (NCT02624947) did not  
645 show the vaccine candidate to be sufficiently efficacious in preventing RSV-  
646 associated medically significant LRTIs during the first 90 days of life (efficacy 39%

97.52% CI -1.0 to 63.7; pre-specified lower boundary of 97.52% CI  $\geq 30\%$ ), although fewer infants within the study group were hospitalized due to RSV-associated lower respiratory tract infections than in the placebo group (2.1% vs. 3.5%, vaccine efficacy 44%, 95% CI 19.6 to 61.5).<sup>156</sup> Animal models and observational human studies have more recently demonstrated the superiority of the pre-fusion form of the F glycoprotein in stimulating the production of neutralizing antibodies against RSV.<sup>157,158</sup> In 2020, Pfizer (NCT04424316) and GlaxoSmithKline (NCT04605159) both commenced Phase 3 studies of their respective recombinant subunit pre-fusion RSV F antigen vaccine candidates, with completion of both studies expected between 2023-24.

#### **4) Vaccines contraindicated during pregnancy**

Vaccines that are not recommended or contraindicated during pregnancy are summarized in Table 4. The inadvertent administration of these vaccines during pregnancy, for example before the woman realizes she is pregnant, is not an indication for termination of pregnancy, however, there should be counselling regarding the potential risks to the fetus.<sup>80</sup>

#### **Table 4. Vaccines contraindicated during pregnancy**

#### **Conclusion**

Maternal vaccination is an effective yet underutilized means of infectious disease prevention for pregnant women and their infants. Pregnant women should be informed of the potential benefits of vaccination for themselves, their fetuses and infants and proactively offered routinely recommended vaccines in order to allow

timely administration prior to the delivery of the infant. Sufficient time should be allowed to address any concerns women may have regarding the safety of these vaccine during pregnancy. Additionally, healthcare providers should be provided with sufficient training to be able to support pregnant women throughout the decision-making process. Currently, it is recommended that all pregnant women should be routinely offered influenza, tetanus and pertussis-containing vaccines. Pregnant women and lactating women, and also women who are intending to get pregnant, should now routinely be offered the COVID-19 vaccine in view of the mounting evidence of its safety.

There are still a number of vaccines under development which may be licensed for use in pregnancy within the next decade. Additional data are needed to determine the long-term safety of newly developed vaccine technologies which have not previously been evaluated in pregnancy, including RNA and non-replicating viral vector vaccine platforms.

687 **Tables**

688 **Table 1.** Summary of vaccine recommended for administration during pregnancy in  
 689 the US (adapted from CDC guidelines<sup>80</sup>)

690

| <b>Vaccine</b><br>Brand name<br>(manufacturer)   | <b>Number of doses</b><br><b>recommended</b> | <b>Recommended</b><br><b>dosing schedule</b><br><b>(gestation)</b>  | <b>Contraindications</b>  |
|--|--|---|---|
| <b>Influenza</b><br>AFLURIA (Seqirus<br>Pty. Ltd), Agriflu<br>(Seqirus Inc.),<br>FLUAD (Seqirus<br>Inc.), Fluarix (GSK),<br>Flublok (Protein<br>Sciences<br>Corporation),<br>Flucelvax (Seqirus<br>Inc.), FluLaval (ID<br>Biomedical<br>Corporation of<br>Quebec), FluMist,<br>Fluvirin (Sequris<br>Vaccines Ltd.),<br>Fluzone (Sanofi<br>Pasteur) | One dose                                     | Vaccine can be<br>administered<br>during any<br>trimester.<br>Administration<br>prior to start of<br>flu season<br>recommended. | Contraindicated in<br>individuals with a<br>history of severe<br>allergic reaction<br>(e.g. anaphylaxis)<br>or life-threatening<br>reaction to a<br>previous dose of<br>an influenza<br>vaccine |

|   |          |  |   |
|---|----------|--|---|
| <b>Tetanus Toxoid,<br/>Reduced<br/>Diphtheria Toxoid<br/>and Acellular<br/>Pertussis (Tdap)</b><br><br>Adcel (Sanofi<br>Pasteur), Boostrix<br>(GSK) | One dose | Between 27 and<br>36 weeks'<br><br>gestation (can be<br>given earlier if<br>indicated e.g. for<br>wound<br>management or<br>pertussis<br>outbreak)<br><br>If no history of<br>prior vaccination<br>and dose not<br>administered<br>during pregnancy,<br>give dose<br>immediately<br>postpartum | Contraindicated in<br>individuals who<br>have had a severe<br>allergic reaction<br>(e.g. anaphylaxis)<br>after a previous<br>dose of a Tdap<br>vaccine or who has<br>a severe allergy to<br>any vaccine<br>component. |
|---|----------|--|---|

691

692

693 **Table 2.** Summary of COVID-19 vaccines, evidence of safety and recommendations694 for use in pregnancy (adapted from Kalafat et al.)<sup>81</sup>

| Vaccine<br>platform | Commercial<br>developer<br>(candidate | Mechanism of<br>action | Assessment of<br>safety in<br>pregnancy | Recommendation<br>s for use during<br>pregnancy |
|---------------------|---------------------------------------|------------------------|---|---|
|---------------------|---------------------------------------|------------------------|---|---|

|      | name)                             |  |  |  |
|------|-----------------------------------|--|--|--|
| mRNA | Pfizer/<br>BioNTech<br>(BNT162b2) | Nucleoside-<br>modified<br>messenger RNA<br>(mRNA)<br>expressed in<br>lipid<br>nanoparticles<br>which encodes<br>the spike protein<br>for SARS-COV-<br>2 virus                   | Real world<br>data<br>from >90,000<br>women has not<br>identified any<br>safety signals<br><br>Pfizer/<br>BioNTech<br>commenced a<br>global Phase 3<br>study | Initial safety data<br>supports safe use<br>of mRNA<br>vaccines in<br>pregnant women |
|      | Moderna<br>(mRNA-<br>1237)        | Nucleoside-<br>modified mRNA<br>encoding the<br>perfusion<br>stabilized spike<br>(S) protein and<br>the S1-S2<br>cleavage site<br>encapsulated<br>within a lipid<br>nanoparticle | recruiting<br>pregnant<br>women in<br>early 2021   |  |
| Non- | Oxford-                           | Modified   | No direct  | No prior studies   |

|                             |                                  |   |                          |  |
|-----------------------------|----------------------------------|---|--------------------------|--|
| replicating<br>viral vector | AstraZeneca<br>(AZD1222)         | chimpanzee<br>adenovirus<br>(replication<br>deficient)<br>containing the<br>gene encoding<br>the spike (S)<br>protein   | safety data<br>available | among pregnant<br>women however<br>adenovirus-<br>vectored Zika<br>vaccine studies in<br>pregnant mice did<br>not identify any<br>safety signals |
|                             | Janssen<br>(Ad26.COV2<br>.S)     | Recombinant,<br>replication-<br>incompetent<br>human<br>adenovirus type<br>26 which<br>encodes the full<br>length of the<br>stabilized<br>conformation of<br>the spike (S)<br>protein |                          |  |
|                             | Sputnik V<br>(Gam-<br>COVID-Vac) | Combined<br>recombinant<br>adenovirus-<br>based vaccine<br>(rAd5 and  |                          |  |

|                         |                       |   |                                 |  |
|-------------------------|-----------------------|---|---------------------------------|--|
|                         |                       | rAd26), both containing the gene encoding the full length spike (S) protein   |                                 |  |
| Protein subunit         | Novavax (NVX-Cov2373) | Stabilized spike (S) protein assembled onto a lipid nanoparticle administered with a saponin-based adjuvant (Matrix-M™) | No direct safety data available | Recombinant vaccines are generally considered safe for use during pregnancy<br><br>Safety of saponin-based adjuvant in pregnancy unknown |
| Inactivated whole virus | Sinovac (CoronaVac)   | Inactivated whole virus particle containing aluminum hydroxide adjuvant   | No direct safety data available | Inactivated vaccines generally considered safe for use during pregnancy.<br><br>Aluminum hydroxide (used in human                        |
|                         | Sinopharm (BBIBP-     | Inactivated whole virus   |                                 |  |

|  |                               |  |  |   |
|--|-------------------------------|--|--|---|
|  | CorV)                         | particle<br>containing<br>aluminum<br>hydroxide<br>adjuvant  |  | papillomavirus<br>(HPV) vaccine)<br>and CpG 1018<br>(used in hepatitis<br>B (HBV) vaccine)  |
|  | Valneva<br>(VLA2001)          | Inactivated<br>whole virus<br>particle<br>containing<br>aluminum<br>hydroxide and<br>CpG 1018<br>adjuvants |  | adjuvants both<br>considered safe<br>for use during<br>pregnancy<br><br>Safety of the<br>Alhydroxyquim-II<br>adjuvant unknown<br>in pregnancy |
|  | Bharat<br>Biotech<br>(BBV152) | Inactivated<br>whole virus<br>particle<br>containing<br>Alhydroxyquim<br>-II adjuvant                      |  |   |

695  
696  
697

698 **Table 3.** Tetanus toxoid vaccination schedule for pregnant women and women of  
699 childbearing age with no or uncertain previous exposure to TT, Td or DTP.<sup>31</sup> Table  
700 reproduced with permission from the World Health Organization.

701

| Dose of TT or Td | When to give | Expected duration of |
|------------------|--------------|----------------------|
|------------------|--------------|----------------------|

| (according to card or history) |  | protection  |
|--------------------------------|--|---|
| 1                              | At first contact or as early as possible in pregnancy      | None  |
| 2                              | At least 4 weeks after TT1                                 | 1-3 years   |
| 3                              | At least 6 months after TT2 or during subsequent pregnancy | At least 5 years                                  |
| 4                              | At least one year after TT3 or during subsequent pregnancy | At least 10 years                                 |
| 5                              | At least one year after TT4 or during subsequent pregnancy | For all childbearing age years or possibly longer |

**Table 4.** Vaccines contraindicated during pregnancy

| Vaccine (platform)   | Reason for contraindication   | Safety considerations  |
|--|---|--|
| Bacillus Calmette-Guérin (BCG) ( <i>live attenuated virus</i> )  | Contains live culture preparation of the Bacillus of Calmette and Guérin (BCG) strain of Mycobacterium bovis      | No harmful effects have been observed in pregnant women however safety in pregnancy has not been formally evaluated <sup>159</sup>   |
| Human papilloma virus ( <i>recombinant virus-like particle</i> ) | No safety data available to support use in pregnancy. Not recommended by CDC for administration during pregnancy. | No evidence of increased risk of adverse pregnancy or fetal outcomes following administration during pregnancy. <sup>160,161</sup><br><br>If inadvertent administration during pregnancy, delay remaining doses until after pregnancy. |
| Measles, mumps and rubella (MMR) ( <i>live</i> )                 | Contains live attenuated mumps, measles and   | No evidence of increased risk of adverse pregnancy   |

|  |   |  |
|--|---|--|
| <i>attenuated virus)</i>                   | rubella viruses   | <p>or fetal outcomes (including congenital rubella syndrome) following administration during pregnancy.<sup>95</sup></p> <p>Pregnancy testing is not recommended before vaccine administration of vaccine, however, recipients are advised not to become pregnant for at least 28 days after vaccine dose.<sup>41,80</sup></p> |
| Varicella ( <i>live attenuated virus</i> ) | Contains live attenuated varicella-zoster virus (VZV)   | <p>Data from Merck/CDC Pregnancy Registry has not identified any increased risk of congenital varicella syndrome.<sup>80,162</sup></p>   |
| Zoster ( <i>recombinant glycoprotein</i> ) | No safety data available to support use in pregnancy. Not recommended by CDC for administration during pregnancy. | <p>Data from Merck/CDC Pregnancy Registry has not identified any increased risk of congenital varicella syndrome.<sup>80</sup></p>   |

**Figure legends**

**Figure 1.** Placental transfer of IgG antibodies from maternal to fetal circulation.

Maternal IgG antibodies are taken up into endosomes within the syncytiotrophoblast cells of the placenta and bind neonatal Fc receptors (FcRn). Following acidification of the endosome, the IgG antibodies are then transcytosed to the fetal side of the syncytiotrophoblast. The endosome fuses with the syncytiotrophoblast membrane and the IgG antibodies are then released into the fetal circulation. The higher physiological pH within the fetal circulation promotes dissociation of the IgG from the FcRn (adapted from Palmeria *et al.*)<sup>163</sup> Figure created with BioRender.com, exported with publication and licensing rights. Original figure held under a Creative Commons license

FcRn = neonatal Fc receptor

IgG= immunoglobulin A

**Figure 2.** Transfer of secretory IgA antibodies from maternal breast tissue to

breastmilk. Dimeric IgA molecules attach to polymeric Ig-receptors (pIgR) on the basolateral membrane of the mammary gland epithelium and are transcytosed through epithelial cells. At the apical cell membrane, the IgA dimer is released into the breastmilk with a portion of the pIgR molecule (the secretory chain) still attached (adapted from Albrecht and Arck).<sup>164</sup> Figure created with BioRender.com, exported with publication and licensing rights. Original figure held under a Creative Commons license

IgA= immunoglobulin A

pIgR= polymeric Ig-receptors

**Figure 3.** Global elimination status of maternal and neonatal tetanus. As of December 2020, 12 out of 59 “at-risk” countries identified by the WHO in 2000 had not yet eliminated the disease.<sup>34</sup> Figure reproduced with permission from the World Health Organization.

Countries shaded in green = Maternal and neonatal tetanus eliminated between 2000 and December 2020

Countries shaded in red = Maternal and neonatal tetanus not eliminated

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